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Are there socio-economic inequalities in utilization of predictive biomarker tests and biological and precision therapies for cancer? A systematic review and meta-analysis

Ruth P. Norris^{1,2}, Rosie Dew², Linda Sharp², Alastair Greystoke³, Stephen Rice⁴, Kristina Johnell⁵ and Adam Todd^{1,2*}

Abstract

Background: Novel biological and precision therapies and their associated predictive biomarker tests offer opportunities for increased tumor response, reduced adverse effects, and improved survival. This systematic review determined if there are socio-economic inequalities in utilization of predictive biomarker tests and/or biological and precision cancer therapies.

Methods: MEDLINE, Embase, Scopus, CINAHL, Web of Science, PubMed, and PsycINFO were searched for peer-reviewed studies, published in English between January 1998 and December 2019. Observational studies reporting utilization data for predictive biomarker tests and/or cancer biological and precision therapies by a measure of socio-economic status (SES) were eligible. Data was extracted from eligible studies. A modified ISPOR checklist for retrospective database studies was used to assess study quality. Meta-analyses were undertaken using a random-effects model, with sub-group analyses by cancer site and drug class. Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each study. Pooled utilization ORs for low versus high socio-economic groups were calculated for test and therapy receipt.

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* Correspondence: adam.todd@newcastle.ac.uk

¹School of Pharmacy, Newcastle University, King George VI Building, King's Road, Newcastle-upon-Tyne NE1 7RU, UK

²Population Health Sciences Institute, Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK

Full list of author information is available at the end of the article



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Results: Among 10,722 citations screened, 62 papers (58 studies; 8 test utilization studies, 37 therapy utilization studies, 3 studies on testing and therapy, 10 studies without denominator populations or which only reported mean socio-economic status) met the inclusion criteria. Studies reported on 7 cancers, 5 predictive biomarkers tests, and 11 biological and precision therapies. Thirty-eight studies (including 1,036,125 patients) were eligible for inclusion in meta-analyses. Low socio-economic status was associated with modestly lower predictive biomarker test utilization (OR 0.86, 95% CI 0.71–1.05; 10 studies) and significantly lower biological and precision therapy utilization (OR 0.83, 95% CI 0.75–0.91; 30 studies). Associations with therapy utilization were stronger in lung cancer (OR 0.71, 95% CI 0.51–1.00; 6 studies), than breast cancer (OR 0.93, 95% CI 0.78–1.10; 8 studies). The mean study quality score was 6.9/10.

Conclusions: These novel results indicate that there are socio-economic inequalities in predictive biomarker tests and biological and precision therapy utilization. This requires further investigation to prevent differences in outcomes due to inequalities in treatment with biological and precision therapies.

Keywords: Precision medicine, Molecular targeted therapy, Immunotherapy, Biological therapy, Pharmacogenomic testing, Drug utilization, Socio-economic factors, Meta-analysis

Background

Traditional cancer treatments (chemotherapy, surgery, and radiotherapy) are subject to inequalities in utilization by socio-economic status [1]. These socio-economic inequalities have persisted over time and exist across cancers, healthcare systems, and treatments [2, 3]. Individuals with a lower socio-economic status are less likely to receive conventional treatments, and this may contribute to poorer cancer outcomes in this group [4].

Increasingly, systemic treatments targeted at cancer biology (e.g., tyrosine kinase inhibitors and monoclonal antibodies) are being integrated into cancer clinical care. These agents are expensive (immunotherapy can cost, in US dollars, \$100,000 per patient annually) and may only have efficacy in selected sub-populations [5]. Hence, stratifying patients by molecular pathology to predict the likelihood of tumor response and adjusting therapy accordingly is now routinely recommended (see, for example, [6]). This move towards biological and precision therapies is reflected in the cancer drug development pipeline; for example, in 2019, 450 new cancer drug candidates were immunotherapies [7].

Socio-economic inequalities in biological and precision therapy utilization remain largely unexplored. Some speculate that using molecular information to target cancer treatment potentially provides a solution to current treatment inequalities [8]. Others argue that novel cancer therapies, because of their cost, disproportionately favor those with more resources and, therefore, may widen inequalities further [9–11].

As novel cancer therapies and their associated predictive biomarker tests offer opportunities for increased tumor response, reduced adverse effects, and improved survival, it is important to understand whether there are inequalities in their receipt [12, 13]. This systematic review and meta-analysis integrated the existing research

to investigate the relationship between socio-economic status and utilization of biological and precision cancer therapies and their associated predictive biomarker tests.

Methods

The review was registered with the international database of prospectively registered systematic reviews, PROSPERO (CRD42019140016), and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] (Additional file 1: Supplementary methods 1).

Search strategy and study selection

Searches were performed in seven databases (MEDLINE, Embase, Scopus, CINAHL, Web of Science, PubMed, and PsycINFO) for articles published between January 1998 and December 2019. This time period reflects the licensing and approval of trastuzumab in the USA—considered a crucial time marker in the precision therapy field. Therapies of interest included the following: targeted therapy (targeting either oncogene addiction or synthetic lethality with activity restricted to tumors with appropriate biomarker status), biologics (where no predictive biomarker is included in the license), and immune checkpoint inhibitors. Therapies targeting hormone receptors were excluded as these agents have been in use since the early 1970s [15]. Search terms covering socio-economics status, tests, and therapies were developed; a full search strategy is available in Additional file 1: Supplementary methods 2. Reference lists of eligible articles were also reviewed.

The inclusion criteria for full-text papers, published 1998 onwards and written in English, were determined as follows in terms of PICOS (Population, Intervention, Comparison, Outcome, and Setting). *Population:* solid tumor cancer diagnosis (any age or sex). *Intervention:*

receipt of either a predictive biomarker test or biological and precision therapy (or both). Studies reporting biological and precision therapies administered with an adjuvant (e.g., chemotherapy) were eligible as long as it was clear how many patients received the biological or precision therapy. Only predictive biomarker tests of pharmacological response to targeted treatment were included. *Comparison*: it was not a requirement that a comparator was reported but where noted, and the following comparator details were extracted—a clinical alternative, no biological and precision therapy and/or predictive biomarker tests, or no treatment. *Outcome*: utilization data reported by a socio-economic status measure (e.g., percent of persons living below the poverty line, median household income). *Setting*: retrospective or prospective observational design (including randomized controlled trials analyzed as observational cohorts). Full inclusion criteria are listed in Additional file 1: Supplementary methods 3.

Screening of titles and abstracts was conducted by one author (RN) only. All articles selected for full-text review were independently checked by a second author (AT). Disagreements were discussed and, if necessary, resolved with a third author (LS). Agreement between reviewers was excellent ($\kappa = 0.93$) [16].

Data extraction and quality assessment

Data was extracted by one author (RN) and checked by another (RD). Disagreements were resolved through discussion with the review team (AG, AT, LS, and RD). In instances of missing or inconsistent data, study authors were contacted. Where there was no response, data was documented as not reported, or the paper excluded. In the event of multiple publications reporting identical or heavily overlapping study populations (e.g., same registry, cancer, stage, age group, and time period), data was extracted from the earliest publication, and where there was more than one publication from the same year, extraction first prioritized the publication reporting an income-based socio-economic measure and, second, one reporting multiple socio-economic measures. If more than one multivariable analysis was conducted, information was extracted from the most comprehensive adjusted model.

Data was extracted on author(s); publication year; country; data source; number in study population; cancer diagnosis time frame, patient age(s), cancer stage, and registry coverage; socio-economic measure and unit; numbers receiving predictive biomarker test/biological and precision therapy, overall and by socio-economic group (numerator and, where available, denominator); comparator(s) (where appropriate); and measures of association for not receiving testing/treatment by socio-economic status (e.g., ORs, 95% CIs, and *p* values). All

eligible studies were quality appraised using a modified version of the ISPOR checklist for retrospective database studies. Focus in particular was paid to data sources, statistical results of interest, and generalizability of conclusions drawn [17]. The tool had ten features each scored as 0, 0.5, or 1 (Additional file 1: Supplementary methods 4). Appraisal was conducted independently by two authors (RN and RD), with disagreements resolved through discussion with a third author (AT), and consensus (AT).

Synthesis of evidence

Data was synthesized using a summary of findings table. Where not reported, percentages utilizing biological and precision therapies and/or predictive biomarker test by socio-economic sub-group were calculated from data reported in the paper or supplied by authors, and unadjusted OR for low compared to high socio-economic status were computed for test/therapy receipt. Studies were heterogeneous in terms of outcome analyses (test/therapy receipt or non-receipt), socio-economic comparisons made, whether ORs (crude or adjusted) were reported, and the variables that any adjusted ORs were controlled for. Unadjusted ORs were therefore computed to enable inclusion of as many studies as possible in a consistent way. “Low” socio-economic status was defined as the lowest socio-economic sub-group in each article and “high” socio-economic status as the top sub-group.

Meta-analyses were performed using random-effects, Mantel-Haenszel methods. These assessed the likelihood of (i) test receipt and (ii) treatment receipt by low socio-economic status. Eligibility criteria for studies to be included in the meta-analysis were as follows: unadjusted low and high socio-economic utilization data for one measure of socio-economic status reported and an independent sampling frame (no data overlap with another study/paper). In the primary analyses, results relating to an income measure (or, failing that, education, or otherwise, the reported measure) were included. This reflected the dominance of USA studies within the evidence base, where there are cost implications for drug access [18]. Where multiple papers included study populations from the same or related databases that overlapped in terms of period of diagnosis/treatment, the publication reporting the largest total number of patients was entered into the meta-analysis.

For predictive biomarker tests, results were grouped by cancer site (breast, colorectal, lung, and melanoma). Those for biological and precision therapies were grouped by drug class (targeted therapy, biologic, and immunotherapy), while separate pre-specified sub-group analyses were conducted for breast cancer, lung cancer, and all other cancers (sub-grouped by cancer type: colorectal, head and neck, hepatobiliary, melanoma, mixed,

renal cell). A final post hoc sub-group analysis was performed for the Surveillance, Epidemiology, and End Results program (SEER) versus non-SEER registry studies. Testing for sub-group differences was computed where appropriate. Two post hoc sensitivity analyses (one involving substituting included studies with those excluded due to overlapping sampling frames and the other exploring USA versus non-USA healthcare settings) were conducted to determine the robustness of the results. The I^2 statistic was calculated to estimate the degree of statistical heterogeneity [19], and funnel plots were produced to assess publication bias in analyses of ten plus studies [20]. Statistical analyses were conducted using RevMan 5.3.

Results

Search results

The search identified 17,047 citations. After removal of duplicates, titles and abstracts of 10,722 records were screened for eligibility. After title and abstract screening, 551 records progressed to full-text review. Overall, 62 papers (reporting 58 independent studies) met the inclusion criteria (Fig. 1) and were included in the review. Eight studies reported utilization data for predictive biomarker tests [21–28], thirty-seven studies (41 papers) reported utilization data for biological and precision therapies [29–65], and 3 studies reported both [66–68]. Ten papers (Additional file 1: Table S1) had no denominator populations or only reported an average measure of socio-economic status (e.g., mean household income), and were excluded from inclusion in the meta-analysis and are not discussed further [69–78].

Study characteristics

The 48 included studies covered 7 cancers, 5 predictive biomarker tests, and 11 biological and precision therapy classifications, of which bevacizumab (12 studies) [41–45, 54–56, 58, 59, 64, 65] and trastuzumab (11 studies) [29–39] were most common. Most studies were in the USA ($n = 42$) [21, 22, 25–35, 40–68], and a majority analyzed SEER registry data ($n = 27$) [21, 22, 25, 29–33, 41, 42, 45, 47, 49, 50, 54–59, 61–64, 66–68] (Additional file 1: Fig. S1). Of the SEER data studies, 19 [29–32, 41, 42, 47, 49, 54–59, 61–64, 68] were SEER Medicare (i.e., included patients ≥ 65). The remaining studies were from Canada (4 studies) [23, 36–38], China (1 study) [39], and Ireland (1 study) [24]. Forty-six studies reported one or more area-based socio-economic status measure, and only two utilized individual-based measures [34, 68]. Six SES measures (poverty, income, education, employment, deprivation, and socio-economic status aggregate score) were reported. For nine studies, utilization was only available as percentages [24, 29, 32, 52, 54, 56, 61, 66,

67]. Study characteristics are summarized in Additional file 1: Table S2.

Seven papers, pertaining to four studies, reported the same data from the same registry [38, 43, 45, 79–82]. Sixteen papers (covering 8 studies) overlapped in their study populations (cancer site, stage, years of diagnosis time frames, patients' age) [29–32, 36, 37, 41–44, 49, 50, 54, 55, 67, 68]. Two studies did not report unadjusted drug and/or test utilization data [40, 58]. This left 38 studies (including 1,036,125 patients) which were included in the meta-analysis [21–29, 31, 33–35, 37–39, 42, 44–49, 51–54, 56, 57, 59–66, 68].

Quality appraisal

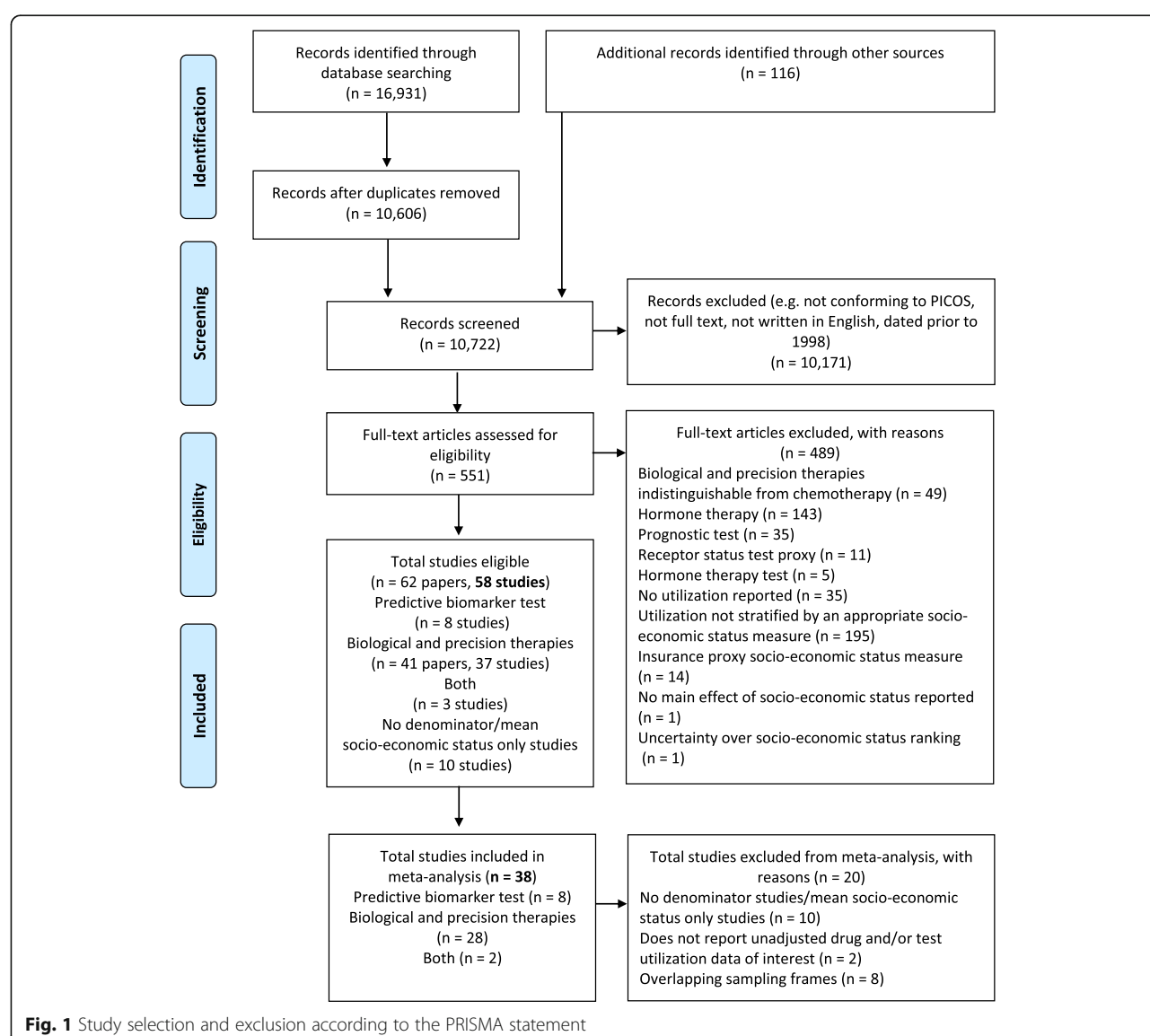
The 48 studies scored in the range 4–10, out of a possible 10 (mean = 6.9, median = 6.5) (Additional file 1: Table S3). Papers scored well regarding data source(s), study populations, and reporting socio-economic definition(s). Discussion of results with reference to the role of socio-economic status, statistical analysis with summary measures like OR, and explanations for confounder selection were often reported poorly.

Predictive biomarker testing

Eleven studies reported data of interest for five predictive biomarker tests [21–28, 66–68]. Ten studies were included in the meta-analysis [21–28, 66, 68]. These covered the following cancers: breast (4 studies) [21–24], colorectal (3 studies) [25–27], melanoma (1 study) [66], and non-small cell lung (2 studies) [28, 68]. The pooled OR for predictive biomarker test receipt for low socio-economic status was 0.86 (95% CI 0.71–1.05; $I^2 = 86\%$; 10 studies) (Fig. 2). This pattern was consistent across cancer sub-groups (4 breast cancer studies, 2 lung cancer studies, and 1 melanoma study) but was only significant in colorectal cancer (0.76, 95% CI 0.65–0.88; 3 studies).

Biological and precision therapies: primary analysis

Association of socio-economic status with biological and precision therapy receipt was reported in 40 studies [29–68]. Thirty of which were included in the meta-analysis [29, 31, 33–35, 37–39, 42, 44–49, 51–54, 56, 57, 59–66, 68]. The overall pooled OR for receipt of biological and precision therapy for patients from low socio-economic status was 0.83 (95% CI 0.75–0.91; $I^2 = 85\%$; 30 studies) (Fig. 3). Sub-group analysis suggested stronger associations with immunotherapy utilization (0.82, 95% CI 0.78–0.86; 7 studies) than other therapy classes (14 targeted therapy and 9 biological therapy studies), but the test for sub-group differences was not significant (Fig. 3). Sensitivity analyses which substituted included studies for excluded studies with overlapping sampling frames confirmed the robustness of results



(0.80, 95% CI 0.72–0.88; $I^2 = 86\%$; 30 studies). Similar results were also observed in sensitivity analyses when only USA studies were considered (0.82, 95% CI 0.74–0.91, $I^2 = 85\%$, 27 studies). For full sensitivity analyses results, see Additional File 1: Fig. S2.

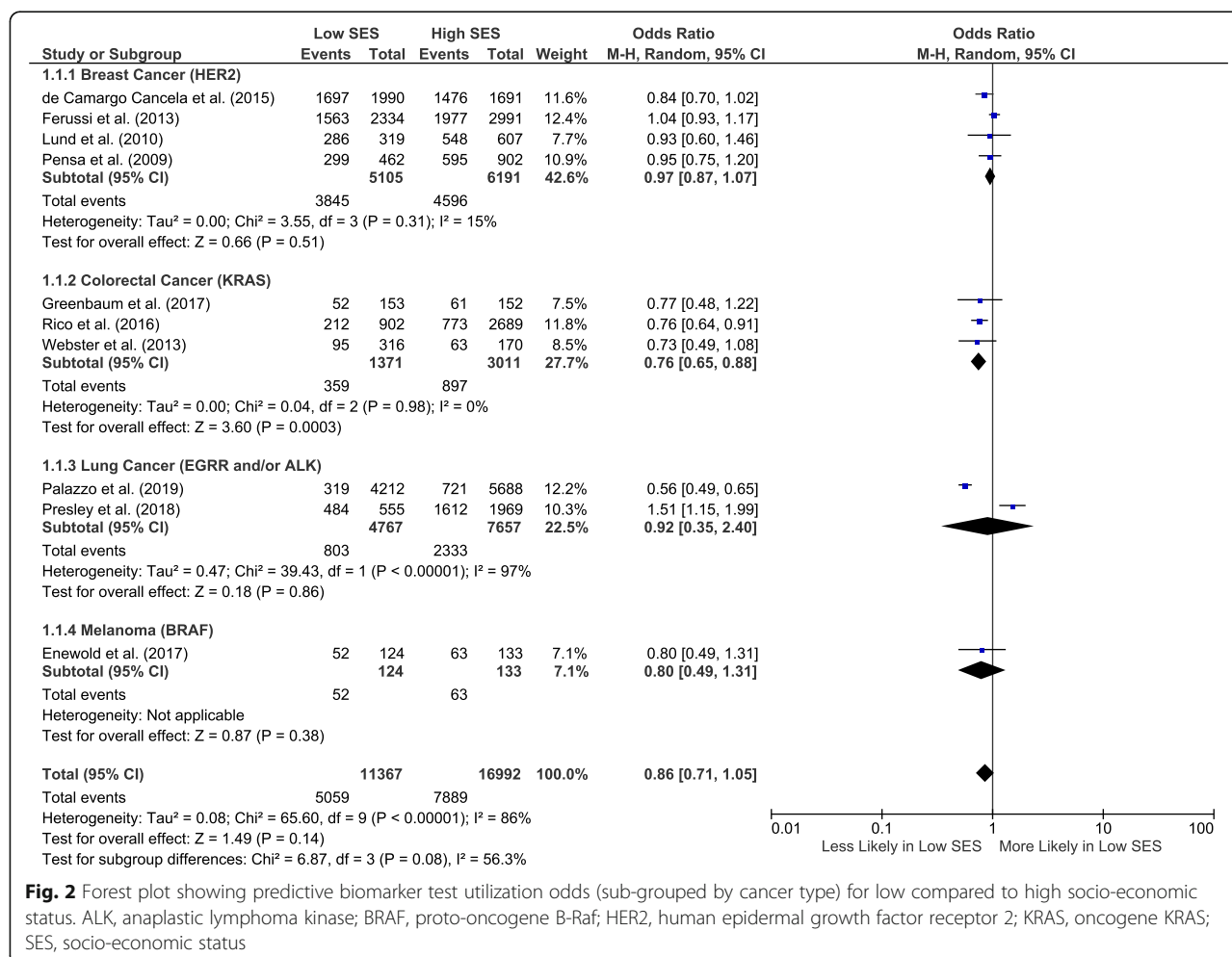
Biological and precision therapies: sub-group analyses

For breast cancer, 11 studies reported the association of socio-economic status with the human epidermal growth factor receptor 2 (HER2) targeting monoclonal antibody trastuzumab [29–39] and one with immunotherapy [40]. Eight studies were eligible for meta-analysis [29, 31, 33–35, 37–39]. The pooled OR for receipt of trastuzumab in those with low compared to high socio-economic status was 0.93 (95% CI 0.78–1.10; $I^2 = 68\%$) (Fig. 4).

Nine lung cancer studies evaluated socio-economic status with biological and precision therapy receipt [41–

47, 67, 68]. Four of these reported bevacizumab [41–44], 2 tyrosine kinase inhibitors [67, 68], 1 both bevacizumab and tyrosine kinase inhibitors [45], 1 immunotherapy [46], and 1 biological therapies (mostly bevacizumab) [47]. Six were eligible for meta-analysis [42, 44–47, 68], and the pooled OR for receipt of biological and precision therapies in those of low compared to high socio-economic status was 0.71 (95% CI 0.51–1.00; $I^2 = 95\%$) (Fig. 5).

Twenty studies reported data of interest for 6 other cancers: hepatobiliary (4 studies) [48–51], melanoma (3 studies) [52, 53, 66], colorectal (8 studies) [40, 54–60], renal cell carcinoma (1 study) [61], and head and neck cancer (2 studies) [62, 63]. A further two studies reported data on more than one cancer [64, 65]. Studies referenced the following 7 treatments: immunotherapy [40, 48, 52, 53, 60], bevacizumab [54–56, 58, 59, 64, 65],



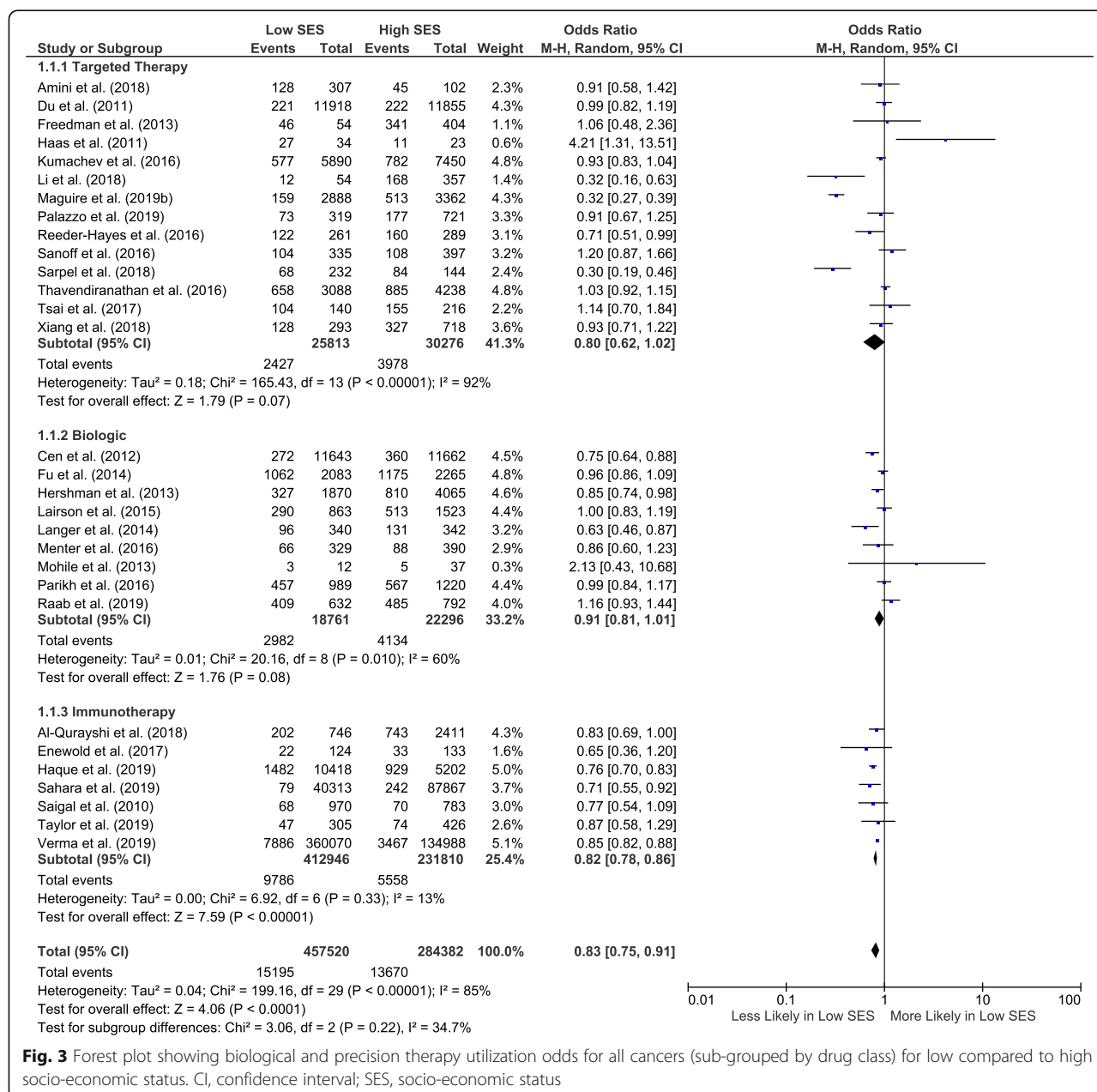
sorafenib [49–51], ipilimumab [66], targeted biologics [57], IL-2 [61], and cetuximab [62, 63]. Sixteen studies could be combined into meta-analyses [48, 49, 51–54, 56, 57, 59–66], giving a pooled OR for receipt of biological and precision therapies for low socio-economic status of 0.84 (95% CI 0.76–0.94; $I^2 = 73\%$) (Additional file 1: Fig. S3). The test for sub-group differences between breast, lung, and all other cancers was not significant (Additional file 1: Fig. S4).

Discussion

This is the first systematic review and meta-analysis to examine whether there are inequalities in novel cancer therapeutics and/or associated testing use. Overall, the findings show that there are statistically significant socio-economic inequalities in biological and precision therapy utilization; those with a low socio-economic status were 17% less likely to be treated with precision therapies. An effect of similar magnitude was observed in test receipt, but did not achieve statistical significance.

The finding that differences are present in novel cancer treatments is consistent with previous systematic reviews documenting traditional treatment inequalities [2, 3]. Similar socio-economic inequalities have also been observed across the cancer care pathway (from screening [83], to diagnosis [84], and timeliness of referral and treatment receipt [85] through to survival [86]). Combined, this suggests that low socio-economic status remains a barrier to treatment access and cancer care, despite advances in treatment.

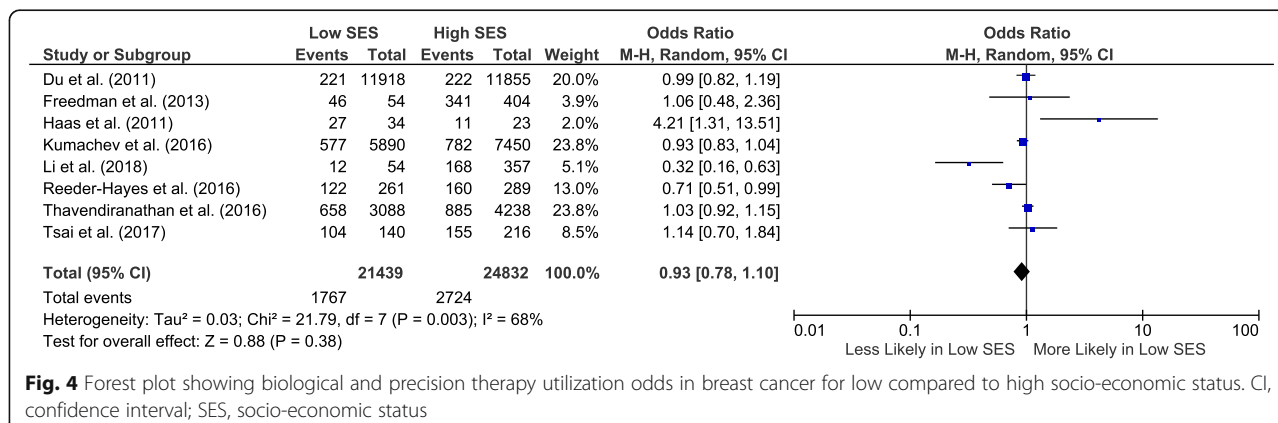
The strength of socio-economic inequalities varied with cancer type: the effect estimate for receipt of biological and precision therapies was stronger for lung cancer (incidence of which is related to low socio-economic status) than other cancers. It is not clear why this is so, although the risk of some cancers (including lung) is associated with health behaviors (e.g., smoking) [87]. It is possible that these health behaviors, alongside other factors (which, themselves may be a consequence of the health behaviors), such as multi-morbidity, could influence a healthcare professional's decision to offer or



initiate, or a patient's choice to receive, cancer treatment [88]. While such individual behavioral factors warrant further investigation, they need contextualizing within the wider determinants of health (i.e., the social, economic, cultural, and clinical level factors) which are also associated with known treatment barriers [89].

The socio-economic inequalities in testing and therapy utilization in breast cancer were less pronounced, despite the majority of research focusing on this cancer. This finding, along with a previous systematic review concluding equivocal associations between socio-economic status and trastuzumab uptake [90], suggests

that low socio-economic status may be less of a treatment barrier in breast cancer, at least as far as newer therapies are concerned. One possible explanation for this may be that breast cancer sub-type differentiation and the practice of hormone receptor status testing, and basing treatment on these results, are well established and routinely embedded in clinical practice (originating in the 1970s following the discovery of the estrogen receptor) [91]. Hence, our findings support the wider concept of the inverse equity hypothesis [92]: that is, that while new interventions may temporarily widen inequalities by disproportionately favoring those with resources



enabling priority access, over time this narrows as treatment access “trickles down” and becomes standard clinical practice [93, 94].

In relation to predictive biomarker testing more generally, the observation that there is reduced utilization with respect to socio-economic status builds on previously documented relationships between factors associated with socio-economic status and test receipt (e.g., negative association between smoking and epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) abnormalities) [95]. Previous work also highlights that test patterns vary temporally and spatially [96, 97], as well as with respect to patient demographics (e.g., age) [98]. This suggests that testing access is complex. Nevertheless, the observation that low socio-economic status may reduce access to testing has important implications. First, utilization barriers occur at points other than just therapy receipt, a finding echoed by Cancer Research UK who highlighted that many colorectal and non-small cell lung cancer patients potentially eligible for targeted treatments did not receive molecular testing [99]. Second, if multiple barriers to novel therapy utilization exist, then sophisticated solutions are likely required to prevent cancer

inequalities widening further. In the first instance, further monitoring of inequalities is required. However, given the rapidly evolving nature of the precision oncology field, and the fact that routine datasets generally lack good data on newly licensed therapies and tests, an appreciation of how such information might be captured in future observational studies is required, especially those that are large-scale and population-based. Analysis of new data sources, rich in biological and precision therapies (e.g., UK’s Systemic Anti-cancer Therapy dataset) or predictive biomarker test information (e.g., USA’s Flatiron Health electronic healthcare records database), may provide the first steps here. Encouragement of data collection to enable audit of treatment access would inform development of solutions to respond to any inequalities noted (e.g., low-income assistance programs, investigating access barriers in problem areas) [9].

This is the first comprehensive meta-analysis on this important and growing area of practice, and brings together data on over 1 million patients. Despite this, the study does have several limitations. First, there are challenges comparing studies reporting different measures of socio-economic status. There was no one consistent measure used, and even when studies appeared

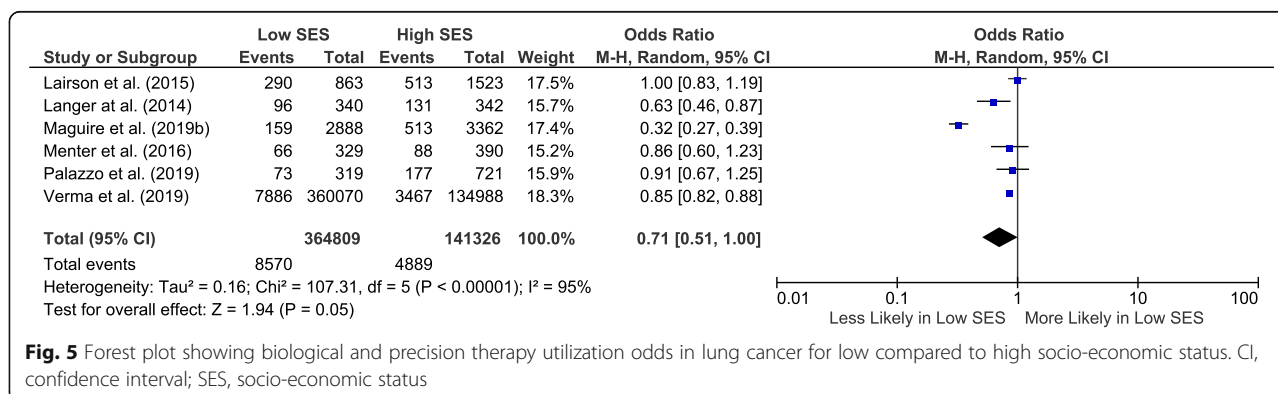


Fig. 5 Forest plot showing biological and precision therapy utilization odds in lung cancer for low compared to high socio-economic status. CI, confidence interval; SES, socio-economic status

to use the same measure (e.g., income), how the variable was categorized (e.g., what was considered “high”; number of sub-groups considered) differed. For most studies, there was considerable variation between what was classified as “high” and “low” socio-economic status, meaning that true differences were unlikely to be attenuated by a lack of variability. However, almost all studies used area-based socio-economic measures, so the ecological fallacy in inference is a risk. Secondly, determining OR from raw data disregards adjustments for confounders; this along with variations in study sampling frames may in part explain the high heterogeneity observed. It also means that the possibility cannot be entirely excluded that any associations seen in the meta-analyses could be explained by uncontrolled confounding. Third, single reviewer title and abstract screening, while considered acceptable by the Cochrane Collaboration [100], may have erroneously excluded relevant studies. Finally, any conclusions drawn here are time specific and may not fully reflect all inequalities present within the system.

The review also highlights limitations in the evidence base. For example, sub-group analyses require care in interpretation where study numbers are small. The majority of studies reported data from non-universal healthcare systems and recorded in SEER Medicare registries. As the relevance of socio-economic indicators varies across the life course, measures such as median household income may be less meaningful in retired SEER populations [101]. In such circumstances, eligibility for Medicare may be more important in addressing one of the most important barriers to care in the USA—that of having health insurance. Similarly, as employment is often tied to insurance coverage in non-universal healthcare systems like the USA, this choice of socio-economic indicator could be an additional factor related to utilization outcomes in the under 65 age group other than income alone. The generalizability of conclusions drawn to patients outside the USA and age groups younger than 65 years must be questioned. Having said this, studies from other countries documented similar patterns in inequality [24, 37, 39]. Moving forward, consideration of data from other registries (e.g., Scandinavian datasets known to be rich in socio-economic detail) would be valuable. The SEER registry also underrepresents minority populations. This limitation may be important given the links between ethnicity and genetics [102–104]. Despite these limitations, among all analyses, there was no clear observable evidence of publication bias (Additional file 1: Fig. S5).

Future research should focus on investigating the reasons for inequalities around these novel therapies. Consideration of testing as a treatment barrier requires prioritization, and work investigating clinician, patient, and family roles in decision-making around testing and

treatment receipt is crucial. This is even more pertinent given the projected increases in panel sequencing testing costs and the growing number of therapeutic agents entering clinical practice. To aid further work in this area, it would be helpful if researchers critically evaluated the relationships between the different measures of socio-economic status in healthcare utilization research: for example, individual versus population measures, single versus aggregate measures, or the various single measures such as education or income. Doing so acknowledges that there is not one standardized, superior socio-economic measure to select. Rather, that as all indicators have limitations and the constraints of current dataset access may restrict the feasibility of further measurement, the magnitude of inequalities observed as well as the ability to make cross-study comparisons requires contextualizing in any future findings. From a practice perspective, policymakers and clinicians need to be aware of the potential barriers to biological and precision therapy beyond patients’ tumor molecular profiles. Revising guidelines to include a focus on reducing inequalities would assist with such prioritization.

Conclusions

There are socio-economic inequalities in the utilization of both predictive biomarker tests as well as biological and precision cancer therapies. This requires further investigation to prevent differences in outcomes due to inequalities in treatment with biological and precision therapies.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12916-020-01753-0>.

Additional file 1: Supplementary methods 1, PRISMA checklist. **Supplementary methods 2**, search strategy. **Supplementary methods 3**, inclusion/exclusion decision trees. **Supplementary methods 4**, quality appraisal tool. **Table S1**, no denominator/mean socio-economic status only study characteristics. **Fig. S1**, SEER versus non-SEER registry studies forest plot and funnel plot. **Table S2**, included studies characteristics. **Table S3**, quality appraisal results breakdown. **Fig. S2**, sensitivity analyses. **Fig. S3**, all other cancers forest plot and funnel plot. **Fig. S4**, breast, lung and all other cancers forest plot and funnel plot. **Fig. S5**, additional funnel plots.

Abbreviations

ALK: Anaplastic lymphoma kinase; BRAF: Proto-oncogene B-Raf; CI/CIs: 95% Confidence interval; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; KRAS: Oncogene KRAS; OR/ORs: Odds ratio; PICOS: Population, Intervention, Comparison, Outcome, and Setting; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; SEER: Surveillance, Epidemiology, and End Results program; SES: Socio-economic status

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Authors' contributions

AG, AT, and LS obtained the funding. AG, AT, LS, and RN conceived the study concept and design. AT, RD, and RN identified the literature and abstracted data. AG, AT, KJ, LS, RD, and RN interpreted the data. RN and SR undertook the statistical analysis. RN drafted the manuscript. All authors read and approved the final draft. AT has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' information

Not applicable

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

¹School of Pharmacy, Newcastle University, King George VI Building, King's Road, Newcastle-upon-Tyne NE1 7RU, UK. ²Population Health Sciences Institute, Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK. ³Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK. ⁴Health Economics Group and Evidence Synthesis Team, Population Health Sciences Institute, Newcastle University, Newcastle-upon-Tyne, UK. ⁵Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

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